Introduction to the "Animal Rule"

Plague Vaccine Workshop
October 13-14, 2004

Mark J. Abdy, DVM, PhD
FDA/CBER
Office of Vaccines Research & Review
Abdy@cber.fda.gov

The Rule was needed because..

In some cases, human efficacy trials may not be feasible nor ethical:

- Epidemiology precludes “field trials”, the usual source of efficacy data, and
- Cannot conduct human challenge/protection studies.

- Which disease forms of plague meet these criteria?

The "Animal Rule"

Approval of Biological Products (New Drugs) When Human Efficacy Studies Are Not Ethical or Feasible

Request For Comments: 62 FR 40996 (July 31, 1997)

Proposed Rule: 64 FR 53960 (Oct 5, 1999)

Final Rule: 67 FR 37988 (May 31, 2002)

21 CFR § 601.90-95 (biologicals)

21 CFR § 314.600-650 (drugs)

To date, only one product – pyridostigmine bromide – has been licensed using the "Animal Rule".

Scope of the "Animal Rule"

Drugs & biologicals that reduce or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances.

Rule does not apply if product approval can be based on standards described elsewhere in FDA's regulations.

FDA may approve a product for which …

- Human safety has been established, and
- "Animal Rule" requirements are met – based on adequate and well-controlled animal studies, the results of which establish that the product is reasonably likely to provide clinical benefit in humans.

- Do we have adequate animal models for plague studies?

Rely on evidence of effectiveness from animal studies only when:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product.

- Do we understand the pathogenesis/pathology of plague reasonably well?
- Do we understand how the plague vaccine prevents disease?

Rely on evidence of effectiveness from animal studies only when:

2. Effect independently substantiated in more than one animal species (some exceptions)
   - Including species expected to react with a response predictive for humans.

- Which animal models (species & strains) are most relevant?
- Does the immune response in animals resemble that of humans?

Rely on evidence of effectiveness from animal studies only when:

3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity.

- Does the disease induced in animals resemble that seen in humans?

Rely on evidence of effectiveness from animal studies only when:

4. Selection of an effective dose in humans
   - Kinetics & pharmacodynamics and/or other relevant data in animals & humans.

   – What components of the immune response are important for protection and how can they best be measured?
   – Need to be able to bridge the immune response data from animals to humans.

GLP & AWA Requirements

All studies subject to this Rule must be conducted in accordance with preexisting requirements under the Good Laboratory Practices (21 CFR § 58) regulations and the Animal Welfare Act (7 U.S.C. 2131).

GLP will be required for the definitive/pivotal animal studies – not necessary for the pilot studies. Also, if you want to mention the animal study in the label, then it should be done according to GLP.

Animals Study Design Challenges

- The label indication. Pre-exposure/post exposure? Bubonic and/or pneumonic?
- Route of exposure. Mimic human exposure routes.
- Endpoints of animal studies. IACUC & EU regs.
- Appropriate challenge dose. Challenge route, species of animal and strain of *Y. pestis*.
- Statistical considerations. Rodents vs. NHP
- Protection against multiple *Y. pestis* strains. If more than one strain – which strains should be tested?

Assays & Immunology

- Considerable R&D may be necessary to develop and validate assays.
- Assay performance data:
  - Validation for both animal & human assays before pivotal/definitive study.
- Immune Response:
  - Must be able to bridge human and animal data.
  - Onset and duration of immunity.

Conclusions

- The “Animal Rule” is new to both industry and to the FDA – collaboration is essential for success.

- Multiple interactions with FDA Advisory Committees
  - In some cases, prior to animal efficacy trials, for concurrence with concepts.
  - Following Agency’s BLA review, prior to approval.

Acknowledgements

Karen Goldenthal, M.D.

Drusilla Burns, Ph.D.

Karen Elkins, Ph.D.

Karen Meysick, Ph.D.